CLINICAL RESEARCH PROTOCOL

A Phase I/II Randomized, Placebo-Controlled, Double-Blind, Single-Center, Tolerability And Preliminary Efficacy Study Of use of Brimonidine Eye Drops for Treatment of ocular Graft-vs-Host Disease (oGVHD)

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Study Product: Brimonidine 0.15%

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SCHEDULE OF VISITS AND PROCEDURES

	Screening	Day 1 (Pre-Dose)	Day 1 (Post-Dose)	Week 3	Week 6	Week 9	Week 12	Week 15
Informed consent	X							
Demographic information	X							
Medical history/ Con Meds	X							
Ophthalmic/ Dry Eye history	X							
Vital signs		X		X	X	X	X	X
Best Spectacle Corrected Visual Acuity		X					X	X
Ocular Surface Disease Index (OSDI)	X	X		X	X	X	X	X
Clinical Global Impression (CGI)				X	X	X	X	X
Subject Global Assessment (SGA)				X	X	X	X	X
Visual Analogue Scale (VAS)			X	X	X	X	X	
Ophthalmic examination (Slit lamp)	X	X		X	X	X	X	X
Schirmer 1 test and Rose Bengal staining	X	X					X	
Keratograph Oculus Redness Score		X			X		X	
TearLab Osmolarity Test		X			X		X	
LipiView II Examination		X			X		X	
Ocular surface Redness (OR) score		X		X	X	X	X	X
External eye and eye lids photographs	X	X		X	X	X	X	X
Pregnancy test (urine)*	X							
First study medication		X						
Drug dispensation visits, with Instruction on study medication self-administration			X	X**	X**	X**		
Adverse Events/ Concomitant Medications		X	X++	X	X	X	X	X

***If applicable ++ AEs only ** If required**

ABBREVIATIONS

AE	Adverse Event
APC	Antigen-presenting cells
BSCVA	Best Spectacle Corrected Visual Acuity
EC	Ethics Committee
CNL	Corneal Neurobiology Laboratory
CRF	Case Report Form
CGI	Clinical Global Impression
DED	Dry Eye Disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IB	Investigator's Brochure
IOP	Intraocular pressure
IRB	Institutional Review Board
KCS	Keratoconjunctivitis sicca
LLT	Lipid Layer Thickness
MAO	MonoAmine Oxidase
MGD	Meibomian Gland Disease
MGE	Meibomian Gland Evaluator
NEI	National Eye Institute
NIKBUT	Non-invasive Keratograph Tear Film Break-Up Time
OSDI	Ocular Surface Disease Index
Otc	Over the counter
BID	Two times per day
SAE	Serious Adverse Event
SGA	Subject Global Assessment
SP	Substance P
TCA	TriCyclic Anti-depressant
TMH	Tear Meniscus Height
UIC	University of Illinois at Chicago
VA	Visual Acuity
VAS	Visual Analog Scale

Study Summary

Title	A Phase I/II Randomized, Placebo-Controlled, Double-Blind, Single-Center, Tolerability And Preliminary Efficacy Study Of use of Brimonidine Eye Drops for Treatment of ocular Graft-vs-Host Disease (oGVHD)
Short Title	Brimonidine treatment for ocular Graft-vs-Host Disease
Protocol Number	UIC-CNBL-2002
Phase	Phase I/II
Methodology	Double-blind
Study Duration	15 weeks
Study Center(s)	Single-center
Objectives	To evaluate the tolerability and preliminary efficacy of Brimonidine Eye Drops for Treatment of ocular Graft-vs.-Host Disease (oGVHD)
Number of Subjects	51 (36 total + 15 screen failures)
Diagnosis and Main Inclusion Criteria	Men and women ≥ 18 years of age with a diagnosis of Meibomian Gland Dysfunction (MGD), and OSD I≥ mild (≥13).
Study Product, Dose, Route, Regimen	Study Drug: Brimonidine 0.15% Eye Drops, 0.15% or 0.075%, administered as eye drops, 2 times a day (b.i.d) for 12 weeks. Control: Refresh plus Artificial Tear dispensed in Brimonidine bottles 2 times a day (b.i.d) for 12 weeks
Duration of administration	12 weeks
Reference therapy	None
Statistical Methodology	One eye (target eye) will be selected at screening visit for statistical comparisons as follows: (i) if only 1 eye meets inclusion criteria, this eye is used; (ii) if both eyes meet inclusion criteria, the eye with the higher RBS score is used; (iii) if both eyes have the same RBS score, then the one with the lower Schirmer I score is used; (iv) if both eyes have same scores, the right eye is used. Secondary analyses will be performed for the non-target eye as well. This trial is primarily descriptive in nature. Descriptive statistics will be used for all primary and safety endpoints, when appropriate. A Wilcoxon test will be used to compare changes in subjective symptoms from Baseline to follow-up values at week 3, week 6, week 9, week 12 and week 15. Primary efficacy measure is the mean reduction in OSDI score between baseline and 12 weeks after 12 weeks of treatment. Primary safety measure is the proportion of patients at week 12 who were able to successfully complete a full twelve weeks of therapy with topical Brimonidine (0.15% or 0.075%) administration two times per day (b.i.d).

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Dry Eye Disease is a disease of the surface of the eye, tear film and related ocular tissues. Millions of people suffer from one form of the disease or another and its prevalence increases with age. Dry Eye Disease sufferers experience a broad range of symptoms including discomfort, irritation, burning, itching, redness, pain, gritty feeling, foreign body sensation, blurred vision and ocular fatigue. These symptoms can progress and lead to ulceration and perforation of the cornea, lead to increased ocular infections and even result in an inability to produce emotional tears.

Dry eye as a disease entity is considered to fall into two broad categories: 1) Aqueous tear deficiency (as seen in Sjögren's syndrome) and 2) increased tear evaporation (evaporative dry eye). Meibomian gland dysfunction (MGD), or posterior blepharitis, is a condition of meibomian gland obstruction and is the most common cause of evaporative dry eye.[1-4] MGD of sufficient extent and degree is associated with a deficient tear film lipid layer, an increase in tear evaporation, and the occurrence of an evaporative dry eye.[1] Meibomian Gland dysfunction can happen with numerous conditions such as Rosacea, Sjögren's syndrome, and oGVHD. In order to limit the influence of differing etiologies on the outcome of this trial, we have limited the screening to MGD that accompanies oGVHD.

Meibomian glands, sebaceous glands in the tarsus of the eyelids, consist of multiple acini emptying into a central duct that opens at the surface of the lid margin just anterior to the mucocutaneous junction. The eyelid margin is for most part lined by the skin. The cornified skin-type epithelium of eyelid margin abruptly changes to non-keratinized epithelium posterior to the opening of the meibomian gland ducts.[5] Blood vessels and nerves are located in deeper layers of skin and in the substantia propria.

Meibomian glands secrete a mixture of lipids and other components that form the outer layer of the preocular tear film. This lipid layer functions to decrease tear film evaporation. Meibomian gland dysfunction (MGD) leads to evaporative dry eye disease. Typical slit lamp biomicroscope findings in MGD include: lid margin telangiectasia, anastomosis of vessels on mucocutaneous junction, poor expression of meibomian secretions by digital pressure, turbid meibum with increased paste like consistency, dropout of meibomian gland acini and obliteration of meibomian duct orificies. One of the most well recognized clinic finding in MGD is the presence of numerous telangiectatic blood vessels coursing across the eyelid margin.

Sensory nerves are strongly implicated in the meibomian gland secretion. The presence of nerve fibers in the meibomian glands distinguishes them from other sebaceous glands, which generally lack innervation.[6] Large subsets of nerve fibers immunoreactive for VIP (marker for parasympathetic nerves) or NPY (localized in parasympathetic and sympathetic nerves) are present, many apposing the basement membrane of meibomian gland acini or surrounding duct structures.[7] Nerve fibers immunoreactive for CGRP (marker for sensory nerves originating in the trigeminal ganglion) and SP are also present in the meibomian glands. Meibomian gland function may be under neural control through direct effects on the synthesis or extrusion of meibomian lipids by the acini or indirectly through vascular dilation, or both.[8] The morphological and functional data support the following hypothesis for

meibomian gland secretion. Stimulation of nerves release neurotransmitters from parasympathetic nerves (acetylcholine and VIP) and sensory nerves (CGRP). Acetylcholine causes meibum secretion by a muscarinic action while CGRP and VIP cause vasodilation, which seems to be a prerequisite for secretion.

Our clinical observations in patients with meibomian gland dysfunction (MGD) lead us to conclude that neuroimmune and neurovascular communication may be the pathophysiological basis of MGD. Clinically MGD is characterized by the presence of prominent telangiectatic vessels on the eyelid margin (vasodilation, not angiogenesis) that probably lead to extravasation of plasma and inflammatory cells in the eyelid tissue and chronic pain. Neuropeptides that are released from sensory nerves (CGRP) or parasympathetic nerves (VIP and NPY) may have caused the vasodilation. CGRP is an extremely potent vasodilator[9] and its action may be contributing to the inflammation seen in MGD. CGRP actions may be abrogated by alpha-2 adrenergic agonist by three methods: (i) vasoconstriction leading to reduced extravasation of fluid and inflammatory cells; (ii) reducing the release of CGRP from afferent nerves in response to excitatory stimulus; and (iii) reducing the expression of CGRP in nerves and keratinocytes.

1.2 Agent

The agent used in this study is a commercial alpha-2 adrenergic receptor agonist, Brimonidine 0.15%or Brimonidine 0.075% (1:1 dilution will be performed using 0.15% Alphagan-P solution with Refresh Plus Artificial Tears solution) applied as eye drops to the eyelid margin in patients with MGD.

Brimonidine tartrate ophthalmic solution is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It has a molecular weight of 442.24 as the tartrate salt, and is both soluble in water and in the product vehicle at pH 7.2.[10] In solution, Brimonidine has a clear, greenish-yellow color. It has an osmolality of 250-350 mOsmol/kg and a pH of 6.6-7.4 (0.15%). Each mL of brimonidine tartrate ophthalmic solution contains: brimonidine tartrate 0.15% (1.5 mg/mL) as the active ingredient. The inactive ingredients include povidone; sodium borate; boric acid; sodium chloride; potassium chloride; calcium chloride; magnesium chloride; mannitol; polyquad 0.001% (0.01mg/mL) as a preservative; purified water; with hydrochloric acid and/or sodium hydroxide to adjust pH. Control group will get placebo (Refresh Plus A1:1 rtificial tears) dispensed in Brimonidine bottles.

1.3 Preclinical Data

No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved 90 and 80 times, respectively, the plasma drug concentration (C_{max}) estimated in humans treated with one drop of brimonidine 0.15% into both eyes 3 times per day. Brimonidine tartrate was not mutagenic or cytogenic in a series of in vitro and in vivo studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.[10]

It is a Pregnancy Category B drug. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Reproductive studies performed in rats and rabbits with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or harm to the fetus due to brimonidine. Dosing at this level produced an exposure in rats and rabbits that is 120 and 60 times higher, respectively, than the exposure seen in humans following multiple ophthalmic doses of

brimonidine.[10] There are no adequate and well-controlled studies in pregnant women. We will not use the drug in pregnant women to avoid any risks to the fetus.

1.4 Clinical Data to Date

Brimonidine 0.15% ophthalmic solution is indicated and currently used for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Brimonidine is a second-line drug for glaucoma, indicated for patients for whom beta-blockers are contraindicated, and is used for the treatment of glaucoma either alone, or concomitantly with other anti- glaucoma medications. Brimonidine topical gel 0.33% is also indicated for persistent facial erythema of rosacea; approval was based on clinically significant efficacy and good safety data from large-scale clinical trials.[11]

We have used Brimonidine 0.15% aqueous solution as eye drops in one patient with severe mixed dry eye disease (severe tear deficiency and MGD) who had extensive conjunctival and eyelid margin redness. After applying Brimonidine, the patient reported decrease in symptoms of ocular discomfort, and there was a significant reduction in conjunctival and eyelid margin redness.

There is ample evidence stemming from use of brimonidine 0.15% eye drops in glaucoma to suggest that it is a safe drug for ocular application, with no significant serious adverse events. The most commonly reported adverse events have included oral dryness, conjunctivits and ocular burning and/or stinging in 1-12% patients across different studies.[12,13]

Although the IRB application study involves a different patient population than the patient population in which brimonidine eye drop is currently used, there is sufficient evidence to suggest that the drug is well tolerated when applied topically to the eyes in this concentration (0.15%) and dose (two times a day). Besides, our anecdotal evidence with its use in a dry eye disease patient suggests that it was also well tolerated and improved signs and symptoms in patients with dry eye disease associated with MGD. Thus, we do not expect any severe adverse events with ocular use of this drug.

1.5 Dose Rationale and Risk/Benefits

Brimonidine 0.15% is currently used topically as eye drops, 2-3 times a day, for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

We will be applying the formulation either as 0.15% or 0.075% (1:1 dilution will be performed using 0.15% Alphagan-P solution with Refresh Plus Artificial Tears solution) topically to the ocular surface as eye drops. One drop will be applied to each eye, two times a day. The drug formulation is being used unchanged, in the doses, route and frequency as is used currently for glaucoma. We do not expect any serious adverse events with this dose. We have chosen twelve weeks duration of therapy as it will give us better data to predict side effects during long-term use.

Several studies have reported the overall safety and efficacy of brimonidine 0.2% and 0.15% after 1, 3 and 4 years. One study demonstrated a reduction in adverse effects with brimonidine 0.15%,[14] but another has shown no difference between brimonidine 0.2% and 0.15%.[15] The most common systemic side effects include dysguesia, fatigue, eye pain, dry mouth and headache.[16-20] The incidence of blepharitis and belpharoconjunctivitis has been reported as 9 – 12.7%,[20-22] follicular conjunctivitis has been found in 7.8 – 12.7% of patients[20,21] and conjunctival hyperemia has an incidence of 5 – 30.3%.[12,13,]

Importantly, brimonidine is contraindicated in children. It has been linked with side effects associated with CNS depression in neonates and infants.[23-26] These effects may occur because children have a less mature BBB to stop brimonidine and prevent CNS effects. There is laboratory evidence that α2-adrenoceptor agonists may potentiate smooth muscle vasoconstriction in arteries,[27] and brimonidine is, therefore, contraindicated in cerebral or coronary insufficiency, postural hypotension and Raynaud's disease.

An allergic reaction to the drug cannot be predicted beforehand. In event of an allergic reaction, the drug will be stopped immediately, and symptoms will be managed appropriately depending on the severity of the reaction.

No psychological, social, legal, or financial risk is expected from participating in the research.

There is always a risk of a loss of confidentiality.

2 Study Objectives

The objective of this study is to establish whether patients with dry eye disease (DED) are able to tolerate receiving Brimonidine: 0.15% eye drops two times a day for twelve weeks (primary tolerability objective) and to investigate the preliminary efficacy of Brimonidine 0.15% topical eye drop solution in treating MGD (primary efficacy objective).

3 Study Design

3.1 General Design

This will be a Randomized, placebo-controlled, double-blind feasibility study, in which a total of 51 (36 + 15 screen failures) patients will be enrolled at 1 clinical site. Subjects will be randomly assigned to one of three groups (#1, #2, or #3) with 17 subjects per group. One group will be given placebo (refresh plus artificial tears) and the other two groups will be given eye drops containing the study drug (Brimonidine: 0.15% or 0.075%).

Patients with established MGD will be approached by a member of the research staff to determine if the patient might be interested in participating in a research study. If the subject is interested, the research staff member will describe the study. If the patient is willing to enter the study, the study will be discussed and the patient will be asked to sign the informed consent form. Screening procedures include documentation of prior MGD. Eligible patients will be enrolled in the study.

All enrolled patients will receive their first dose of the test medication (study drug Brimonidine: 0.15% or 0.075%) or placebo (refresh plus artificial tears)) on study Day 1 in the doctor’s office, and after completion of the study assessments, will have the topical eye drops dispensed for self-administration. See Section 5.4 *Preparation and Administration of Study Drug* for details.

Subjects will be provided with diaries to record the time of each dose and will also be asked to record any adverse symptoms. In addition, they will be asked to make a note of any missed doses together with the reason for the omission. Subjects will return three weeks later on Day 21 for further study

assessments, thereafter at 6 weeks, 9 weeks and 12 weeks (the last day of treatment), and again at 15 weeks after three weeks of no treatment with study drug for the final study assessments.

3.2 Primary Study Endpoints

Primary Efficacy End Point: The primary efficacy end point is a mean reduction in OSDI (Ocular Surface Disease Index) score between baseline and 12 weeks after 12 weeks of treatment.

Primary Tolerability End Point: The change in the test substance tolerance between Day 1 (post-dose) and at weeks 3, 6, 9 and 12.

3.3 Secondary Study Endpoints

The secondary study endpoints will include:

1. Change in ocular surface/lid margin staining score as measured by Rose Bengal/Fluorescein dye staining
2. Change in tear secretion as measured by Schirmer I test
3.
4. Change in Keratograph Ocular Bulbar Redness Score
5. Change in lid margin vascularization/telangiectasia
6. Clinical Global Impression (CGI) of change in symptoms from baseline (physician's rating)
7. Subject Global Assessment (SGA) of overall change from baseline (subject's rating)

3.4 Exploratory Study Endpoints

Exploratory endpoints will include:

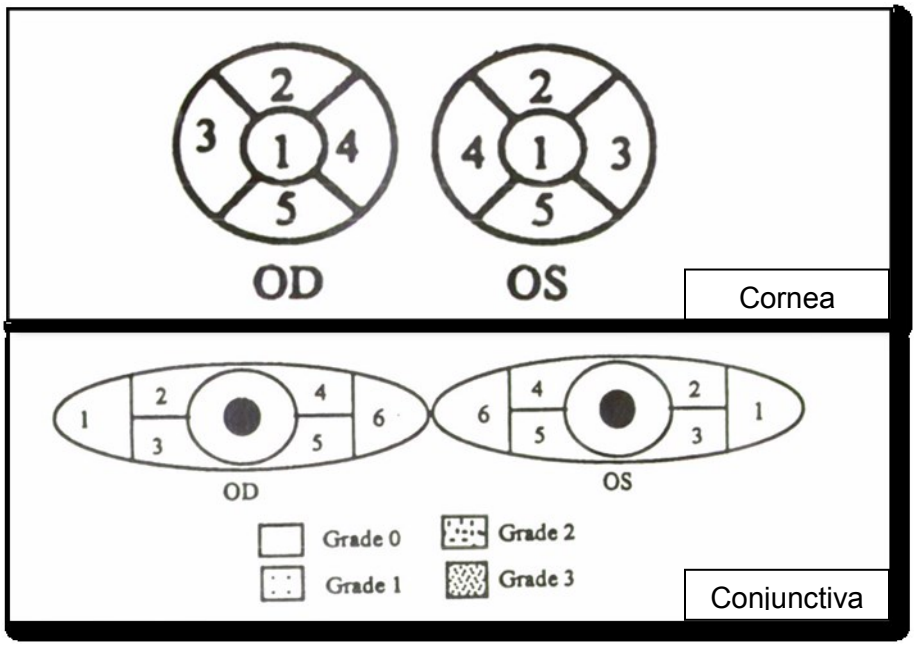
1. No. of visible meibomian gland orifices, and alteration (capping/ obliteration) of the orifices
2. Meibum expression and quality of expressed meibum
3. Eyelid margin changes- thickening, hyperkeratinization, irregularity and muco-cutaneous junction shift
4. Ocular surface redness score
5. Change in Non-Invasive Keratograph Tear Break-Up Time
6. Change in Tear Meniscus Height
7. Change in Tear Fluid Osmolarity
8. Change in Lipid Layer Thickness
9. Change in Meibomian Gland Drop-Out
10. Change in partial or complete blink
11. Change in frequency of blinks
12. Visual acuity change
13. Change in frequency of administration of artificial tears or concomitant eye drops
14. Measurement of number and type of cells (particularly leukocytes) in tear film.

3.4.1 **Efficacy End Point: Meibum expression and quality of expressed meibum**

During a slit-lamp evaluation, the degree of ease in expressing meibomian secretion (meibum) and quality of expressed meibum will be evaluated semiquantitatively as follows: grade 0, clear meibum that is easily expressed; grade 1, cloudy meibum that is expressed with mild pressure; grade 2, cloudy meibum that is expressed with more than moderate pressure; and grade 3, meibum cannot be expressed even with the hard pressure.[28]

3.4.2 Efficacy End Point: Ocular surface Rose Bengal dye staining score

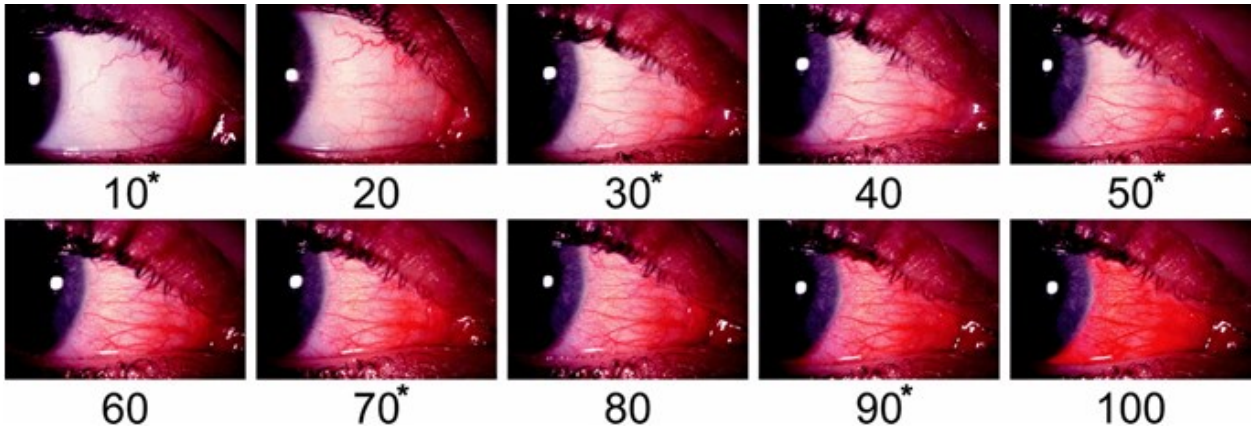
Ocular surface staining will be assessed using Rose Bengal dye. Saline moistened 1% Rose Bengal dye impregnated strips will be used to instill the dye on the conjunctiva and scoring of corneal and conjunctival staining will be performed by a slit lamp examination after 15 seconds using the grading system described by the 1995 NEI workshop.[29] Corneal staining will be graded in 5 zones and conjunctival staining will be graded in 6 zones. Additionally, staining of lid margins will be recorded. Each zone will be graded from 0 to 3 based on the density of punctate staining. The final staining score will be the sum of individual scores from all zones. The scoring pattern is represented below.



3.4.3 Efficacy End Point: Ocular surface redness score

Ocular surface redness (nasal or temporal) will be assessed using the Validated Bulbar Redness grading scale (VBR).[30] The VBR consists of a set of ten images illustrating different degrees of ocular surface redness (OR), ranging from normal to severe, and each image is assigned a value in an order of ascending severity. Colored copies of these images will be made and put up in all the examination rooms. Subjects will be examined by a slit-lamp at 10X magnification using direct diffuse illumination (slit fully opened, angled at 30°- 50° approximately; at half illumination intensity with rheostat set to maximum voltage) and the bulbar conjunctival injection of the subject's eye (nasal and temporal) will be compared to the reference images and graded accordingly. To maintain uniformity, all subjects will be graded by a single physician (Principal Investigator) under constant illumination conditions. The subjects will be asked to look at nasal or temporal fixation marks while the physician will examine the temporal or nasal bulbar conjunctivae, respectively.

Photographic anchors and their respective grades for ocular surface redness are shown below:



3.4.4 Efficacy End Point: Ocular Surface Disease Index (OSDI)

The OSDI rating scale has twelve questions in three discrete areas, with responses rated on a five point scale. Subjects will complete this scale on Day 1 prior to first dose (Baseline), week 3, week 6, week 9, week 12 and week 15. The questions and scoring system are shown below:[31]

HAVE YOU EXPERIENCED ANY OF THE FOLLOWING DURING THE LAST WEEK:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred Vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

HAVE PROBLEMS WITH YOUR EYES LIMITED YOU IN PERFORMING ANY OF THE FOLLOWING DURING THE LAST WEEK:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer Or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS DURING THE LAST WEEK:

	All of the time	Most of the time	Half of the time	Some of the	None of the time	

				time		
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with Low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

3.4.5 Efficacy End Point: Clinical Global Impression (CGI)

At each visit, the physician (Principal Investigator) will use his clinical evaluation (all signs and symptoms taken together) to provide a global assessment of the subjects' change in symptoms and signs. The CGI is a follows:[32]

Question (to physician): In general, compared with the subjects' symptoms and signs at baseline, how would you characterize his/ her overall signs and symptoms now?

The responses will be categorized on a seven point scale as follows:

Marked worsening
Moderate worsening
Minimal worsening
Unchanged
Minimal improvement
Moderate improvement
Marked improvement

Efficacy End Point: Subject Global Assessment (SGA)

At each visit, the subjects will be asked to assess their overall change from baseline. The SGA is as follows:[32]

Question 1 (to subject): Compared with your first visit, how are your eye symptoms now?

The responses will be categorized on a five point scale as follows:

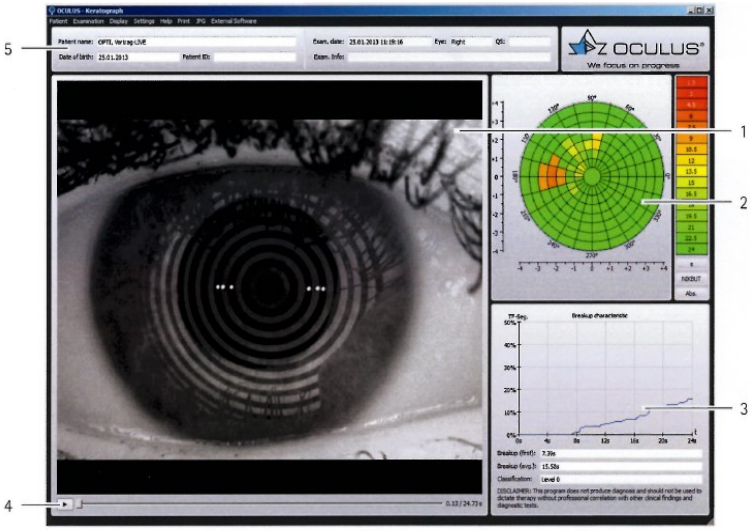
Much worse
Worse
About the same
Improved
Much improved

3.4.6 Efficacy End Point: Keratograph Oculus Redness Score

Keratograph is FDA approved and is used in routine clinical care of patients in the US. The Oculus Keratograph 5M performs a non-invasive tear film analysis. It uses a Placido bowl with a camera aperture that has a fixation mark in the center. The device provides consistent illumination, allowing scanning of the exposed bulbar conjunctiva to take place. The keratograph then analyzes the scanned area. This system generates a BR score automatically, which is based on the area percentage ratio between the vessels and the rest of the analyzed area. For instance, if the ratio is 16%, then the score is 1.6. The maximum ratio, according to the manufacturer, is 40%; therefore, the BR scores that the machine generates range between 0.0 and 4.0.

Non-invasive Keratograph Tear Film Break-up Time (NIKBUT)

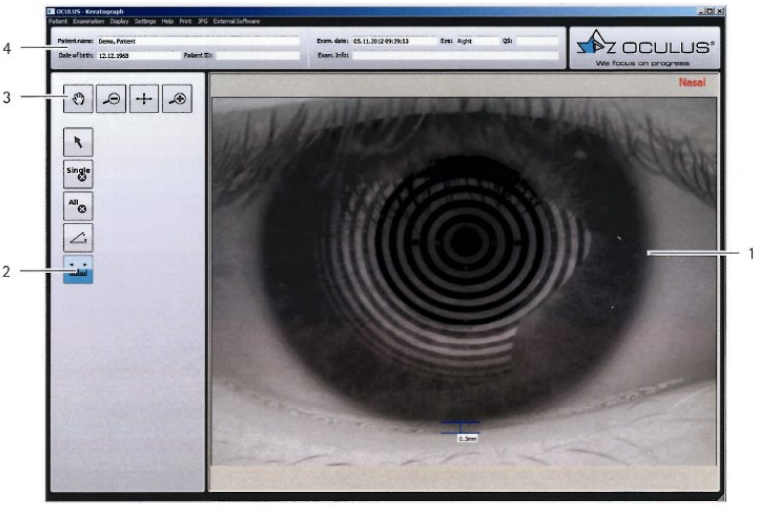
The non-invasive Keratograph tear film break-up time (NIKBUT) measures tear film stability. The NIKBUT is automatically measured within seconds, without fluorescein application. Tear Break-up Time (TBUT) will be measured twice for each eye using IR video derived from the Oculus noninvasive Keratograph tear breakup time (NIKBUT) tool. Based on the device IR video, the device generates 2 measures for TBUT: NIKBUT-first (time at which the first breakup of tears occurs) and NIKBUT-average (average time of all breakup incidents) automatically and without touching the eye.



1 *Camera image*
2 *Color map of the tear film break-up time*
3 *Graphic display of the tear film break-up time characteristics*
4 *Start-stop function for the video with time display*
5 *Examination and patient data*

Tear Meniscus Height (TMH)

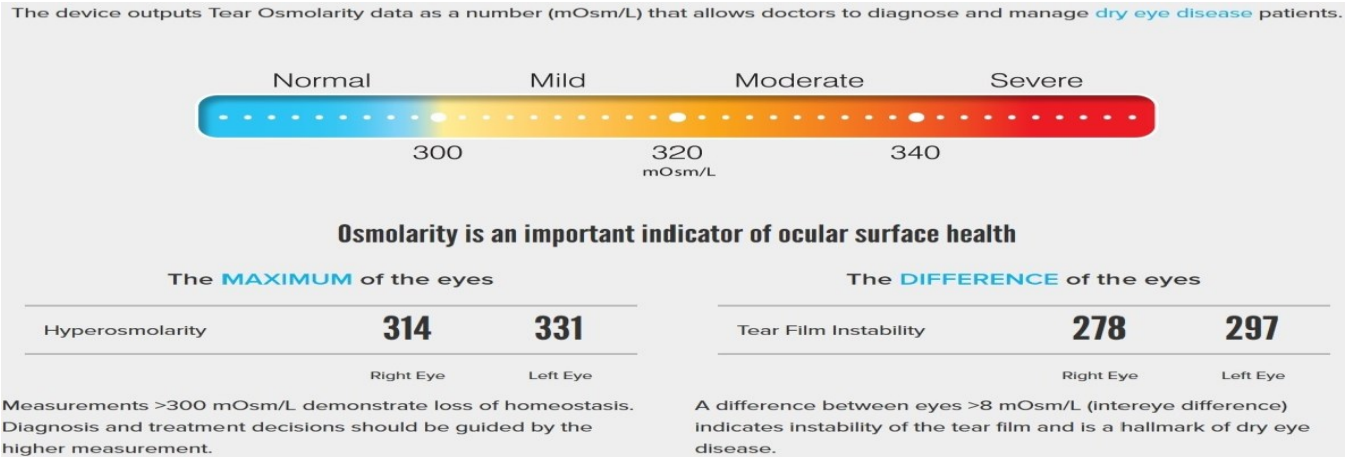
Tear Meniscus Height (TMH) Measurement evaluates the course of the tear meniscus along the eyelid by means of the new infrared illumination and precisely measure the tear meniscus height with an integrated ruler. The TMH is measured twice for each eye using IR images derived from the Oculus TMH tool, The TMH will be graded perpendicular to the lid margin at the central point relative to the pupil center. Oculus TMH measurement is generated automatically by Oculus K5M software. The tear meniscus measurement is important for determining the tear film quantity.



1 *Camera image*
2 *Buttons for tear meniscus measurement*
3 *Buttons to work in the camera image*
4 *Examination and patient data*

3.4.7 Efficacy End Point: TearLab Osmolarity Test

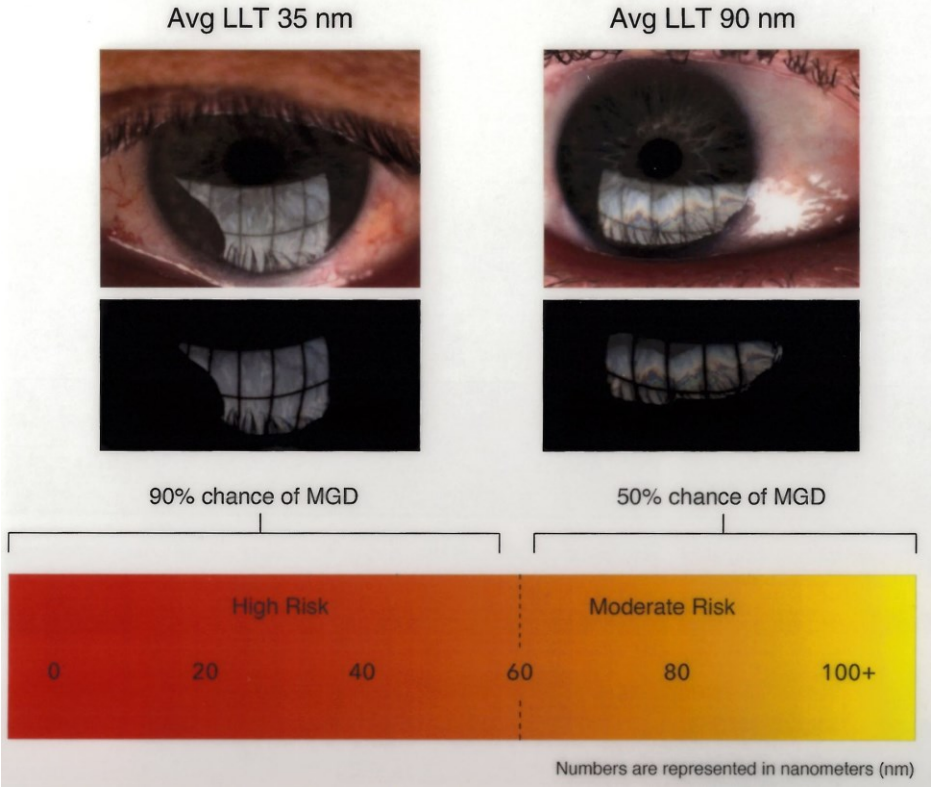
TearLab Osmolarity Test is FDA approved and is used in routine clinical care of patients in the US. The TearLab Osmolarity Test is intended to measure the osmolarity of human tears to aid in the diagnosis of dry eye disease in patients suspected of having dry eye disease. Abnormal tear osmolarity is a failure of homeostatic osmolarity regulation, a key feature of dry eye disease (DED). When left unchecked, hyperosmolar tears in early stage DED will lead to damage of the cornea and conjunctiva evident in later stage disease. The higher the osmolality, the more severe the dry eye. The TearLab Osmolarity Test provides a quick and simple method for determining tear osmolarity using nanoliter (nL) volumes of tear fluid collected directly from the eyelid margin. The TearLab Osmolarity Test utilizes a temperature-corrected impedance measurement to provide an indirect assessment of osmolarity. After applying a lot-specific calibration curve, osmolarity is calculated and displayed as a quantitative numerical value.



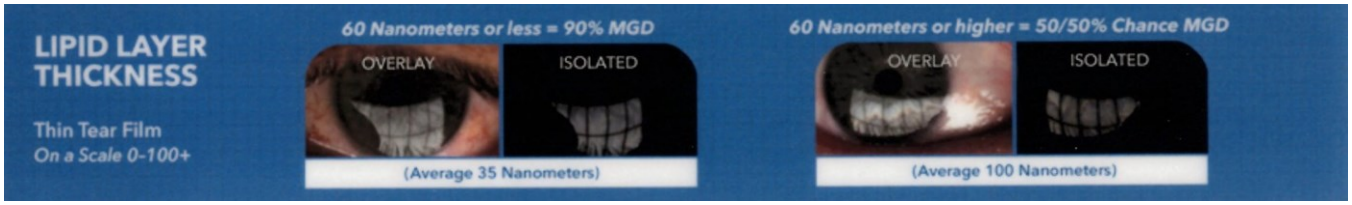
3.4.8 Efficacy End Point: LipiView II Examination

LipiView II images meibomian glands with Dynamic Meibomian Imaging (DMI), which simultaneously employs Dynamic Reflected Illumination and Adaptive High-definition Transillumination. Each technology generates its own independent image of glands, which is then processed, displayed, and combined to provide a more accurate visualization of meibomian gland structure.The LipiView II improves diagnosis of Meibomian Gland Dysfunction (MGD) with objective examination of lipid thickness, blink rate, and meibomian gland structure. The LipiView II is the only instrument that accurately determines lipid deficiency and detects MGD in its earliest stages.

LipiView II Lipid Layer Thickness

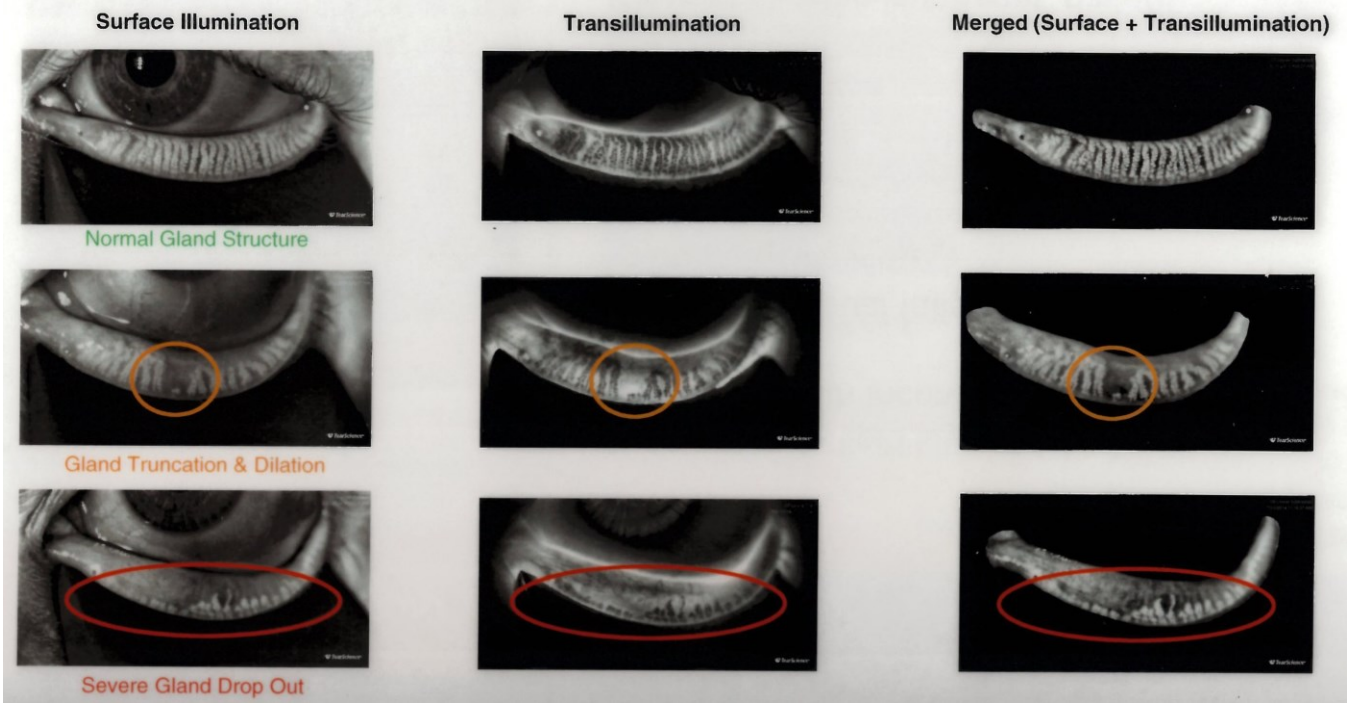


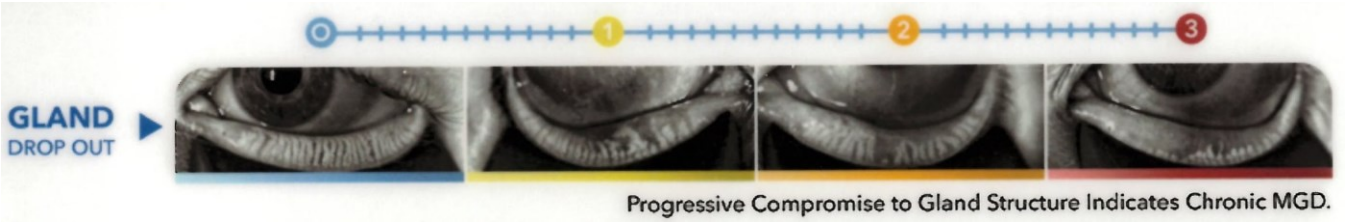
Avg LLT - **Average Lipid Layer Thickness (LLT) in nanometers (nm). Number less than 90 indicates increased probability for MGD.**



LipiView II Gland Drop Out Grade

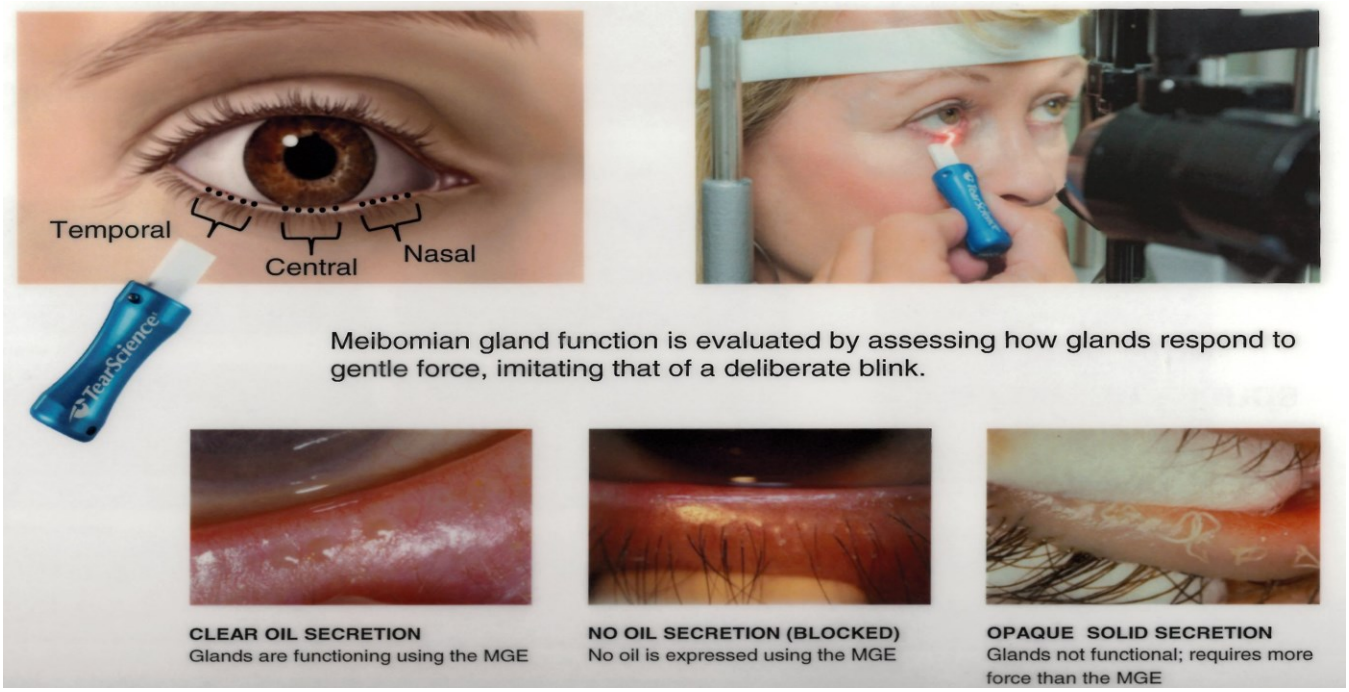
Meibomian gland structure is observed with Dynamic Meibomian Imaging (DMI). DMI produces three images (surface illumination, transillumination and merged) to capture a comprehensive view of Meibomian gland structure.If left untreated, the glands can shrink and deteriorate. The loss of glands is unlikely to be reversible. Failure to treat blocked glands is likely to lead to further structural compromise.

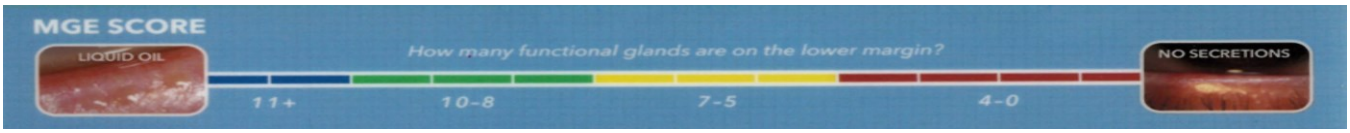




LipiView II Meibomian Gland Evaluator

The Korb Meibomian Gland Evaluator (MGE) is the only instrument that provides a standardized, repeatable evaluation of meibomian gland function. By applying a standardized force simulating the pressure of a deliberate blink eye care physician is able to observe meibomian gland functionality through a slit lamp. The Korb MGE verifies the presence of MGD and allows eye care professionals to track disease progression and treatment response. By accurately assessing gland function, the Korb MGE supports the development of a treatment plan through an increased understanding of the presence and severity of MGD. The evaluation takes approximately two minutes per eye and fits easily into a routine eye exam.



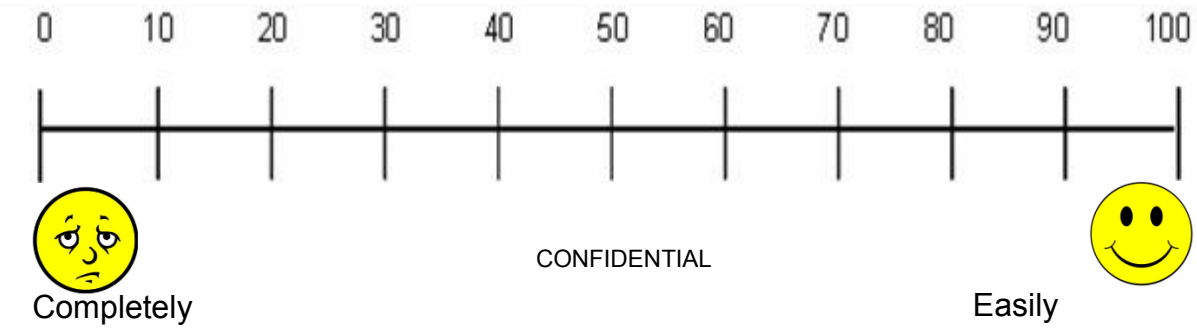


3.4.9 Tolerability End Point: Test Substance Tolerance (Visual Analogue Scale)

Subjects will assess their tolerance to the administration of the study drug, utilizing a Visual Analog Scale (VAS). The VAS is a 100 mm horizontal line with verbal descriptors at either end. The VAS ratings will be completed after administration of the study drug on Day 1 (post-dose), week 3, week 6, week 9 and week 12. Subjects will place a single slash mark across the horizontal line between the end labeled “completely intolerable” (0 mm) and “easily tolerable” (100mm). The VAS rating is as follows:
Please rate the degree of comfort or lack of comfort associated with administering the eye drop by making one slash mark on the line below:

Visual Analogue

On the scale of 0 to 100 seen below, please mark where you would rate your tolerability to administration of the study drug.



3.5 Safety Endpoints

Safety assessments include Vital Signs, recording of all complications and adverse events, as well as ophthalmic exam findings. All ocular and non-ocular adverse events will be assessed for severity and relationship to the investigational product.

Primary safety endpoint:

- The proportion of subjects at week 12 who were able to successfully complete a full twelve weeks of therapy with topical administration two times per day (b.i.d.)

Secondary safety endpoint:

- All adverse events reported, whether deemed related to treatment, or not.
- Clinically significant changes in vital signs or ophthalmic examination from baseline.

3.5.1 Vital Signs

Vital signs will be obtained and recorded at the Day 1 Visit, prior to the first administration of the study drug and on week 3, week 6, week 9, week 12 and week 15. The following vital signs will be measured: 1) blood pressure measurements (mm Hg) will be taken while the subject is relaxed in a sitting position for at least 3 minutes with the arm at heart level. 2) Heart rate will be measured via palpation of a peripheral pulse and will be recorded in beats per minute (bpm). 3) Body temperature (forehead) will be recorded in degrees Fahrenheit (^{0}F).

Clinically significant negative changes from baseline will be recorded on the adverse event forms.

3.5.2 Ophthalmic Examination

At all visits, the Investigator will conduct a complete undilated examination of the eyes using a binocular slit lamp. The Investigator will examine the tear film, eye lids, lashes, bulbar and palpebral conjunctiva, upper and lower lid puncta, cornea, anterior chamber, iris, lens, and anterior vitreous. Specific signs that will be recorded include: lacrimal sac area erythema, swelling or tenderness; no. of and morphological alteration of meibomian gland orifices, lid margin vascularizatuion (including telangiectasia and muco-cutaneous anastomosis), lid margin hyperkeratinization, irregularity and muco-cutaneous junction shift, expressivity of meibum by meibomian glands and quality of expressed meibum, froth or debris or mucous strands in tear film; eyelid hyperemia; punctal hyperemia or atresia; conjunctival/ episcleral hyperemia; papillary or follicular conjunctival reaction; chemosis, episcleral edema; superficial punctate keratopathy, corneal scar, corneal neovascularization; presence and number of corneal filaments, presence or absence of mucoid films, anterior chamber cell, flare or KPs; pupil shape abnormalities, anterior or posterior synechiae, iris neovascularization; lenticular opacities; vitreous cells or pigment. Conjunctival hyperemia (ocular surface redness) will be graded at each visit using the VBR grading system as explained in section 3.3.3. Also, measurement of visual acuity (BCSVA), manifest refraction and intraocular pressure will be performed. Clinically significant changes from baseline examination will be recorded on the adverse event forms.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Patients will be eligible for the study if all of the following criteria are met:

1. Aged 18 years or older.

2. Capable of giving informed consent and does provide informed consent.
3. Diagnosis of Meibomian Gland Disease
4. Women must be post-menopausal ≥ 1 year, or surgically sterilized. If not, a negative urine pregnancy test is required within 7 days of receiving her first dose of study drug along with definite evidence of contraceptive use during the duration of the study. Women of reproductive age should use a method of birth control that is acceptable to the subject and the study doctor. This may include oral contraceptive pills, birth control implants, barrier methods or abstinence. If a subject mentions she suspects she may be pregnant after being enrolled, another pregnancy test will be administered. If the test is positive, she will be discontinued from the study immediately.

4.2 Exclusion Criteria

Subjects will not be eligible for the study if any of the following criteria are met:

1. Allergic to Brimonidine or any similar products, or excipients of Brimonidine
2. Currently receiving any Brimonidine preparation as a part of glaucoma management
3. Receiving or have received within 30 days any experimental systemic medication.
4.
5.
6. Active ocular infection or ocular allergies.
7. Any history of eyelid surgery or ocular surgery within the past 3 months.
8. Corneal epithelial defect larger than 1 mm^2 in either eye.
9. Have active drug/alcohol dependence or abuse history.
10. Vulnerable populations, such as neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations.

Subjects will be permitted to continue all their dry eye treatments, including the use of cyclosporine, corticosteroids, artificial tears, eyelid massage, contact lenses or warm compresses.

4.3 Subject Recruitment and Screening

Potential subjects will be recruited from the clinical practice of the investigator at the time of their routine eye examination visit. The clinical practice is located in the Illinois Eye and Ear Infirmary, Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago (UIC). Subjects will include patients who have been diagnosed with MGD in the investigator's eye clinic (cornea clinic or the comprehensive eye clinic), in the Illinois Eye and Ear Infirmary. All subjects will be screened, recruited, and will attend all study related visits only at the PI's clinic in Illinois Eye and Ear Infirmary.

Patients with diagnosed MGD and annoying or activity limiting visual symptoms will be approached by a member of the research staff to determine if the subject might be interested in participating in a research study. If the subject is interested, the research staff member will describe the study. If the subject is willing to enter the study, the study will be discussed and the subject will be asked to sign the informed consent form. Screening procedures include documentation of MGD as well as other assessments as detailed in section 6.5.1. Eligible subjects will be enrolled in the study.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. Where possible, subjects will be followed for safety and encouraged to return for follow-up visits for any unresolved safety events.

The IRB and Investigator also have the right to withdraw subjects from the study for the following reasons: when continuation may jeopardize the health of the subject, protocol violations, adverse events or concurrent conditions, administrative or other reasons.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws from the study prior to 12 weeks, the subject will be asked to complete the procedures outlined in the 12 weeks visit, as soon as possible. Subjects who voluntarily withdraw from the study between week 12 and week 15 will be asked to complete procedures outlined in the week 15 visit as soon as possible. Subjects who are withdrawn due to adverse events will be followed at least until resolution or stabilization of the adverse event.

If the subject remains in the study for safety evaluation, follow-up visits will be scheduled according to the schedule of visits and procedures found in the synopsis.

5 Study Drug

5.1 Description

The study drug, Brimonidine 0.15%, will be supplied as an ophthalmic solution for administration as topical eye drops. Each subject will receive the study drug as a single eye drop in each eye two times a day (BID) for twelve weeks. Except for the first dose on Day1, subjects will self-administer the study eye drops at home. The control group will receive placebo (refresh plus artificial tears) eye drops. Placebo will be dispensed in Brimonidine bottles.

Each subject will receive either study drug Brimonidine (0.15% or 0.075%) or placebo (refresh plus artificial tears), as a single eye drop in each eye two times a day (BID) for 12 weeks. Except for the first dose on Day1, subjects will self-administer the test medication eye drops at home.

Subjects will not be charged for the study drug in any way (neither the cost of the medication nor its dispensing cost).

5.2 Treatment Regimen

Study drug (Brimonidine eye drops) will be applied to both eyes b.i.d for 12 weeks. Placebo (Refresh plus artificial tear) will be applied to both eyes b.i.d for 12 weeks.The subject will be instructed to instill the first dose of the study medication in the morning at approximately 8 a.m., and then the next dose at approximately 12 hour interval. Therefore, doses will be scheduled at approximately 8 a.m. and 8 p.m.

5.3 Method for Assigning Subjects to Treatment Groups

This Randomized placebo-controlled, double-blind study will have three treatment groups. Subjects will be randomly assigned to one of three groups (#1, #2, or #3). Two groups will receive the study drug (either Brimonidine 0.15% or Brimonidine 0.075%), and the other group will receive placebo (Refresh plus artificial tears). We will use a computer-based random code generator (Research Randomizer; http://randomizer.org/) to generate 1 set of 51 non-unique, unsorted numbers with a range from 1 to 3 representing the group number (#1, #2, or #3). A subject identification number will be assigned to each subject once eligibility is confirmed. Based on the randomizer generated table, subject #1 will receive either placebo or study drug. This will be repeated for each subject. For reproducibility purpose, we will document the final randomization schedule and the random SEED number used to generate the schedule. Randomization will be performed by the Illinois Eye and Ear Infirmary's pharmacy

The subject identification number will be used on all study-related documents. To maintain confidentiality, the subject's name will not be recorded on any study document other than the informed consent form and the case report forms. The drug vial .number will be linked to the patient identification number.

5.4 Preparation and Administration of Study Drug

The study drug will be stored and dispensed from the UIC Eye and Ear Infirmary (EEI) Pharmacy. No modifications will be made to the study drug constituents or its packaging. The drug will be dispensed as is marketed for ophthalmic use (5 mL in 8 mL bottles). Two dose groups of brimonidine will be used : 0.15% and 0.075%. 1:1 dilution for Brimonidine (0.075%) will be performed using 0.15% Alphagan-P solution with Refresh Plus Artificial Tears solution. The dilution will be done at Illinois eye and ear infirmary (EEI) pharmacy. The dispensing will be done at Illinois eye and ear infirmary (EEI) pharmacy, under standard aseptic precautions. The eye droppers will be used by subjects as multiple-dose applications. The drug is regularly stored at room temperature (15°-25° C/ 59-77°F).

Instructions for Drug Use:

1. Wash your hands thoroughly with soap and water.
2. Check the dropper tip to make sure that it is not chipped or cracked.
3. Avoid touching the dropper tip against your eye or anything else – eye drops and droppers must be kept clean.
4. While tilting your head back, pull down the lower lid of your eye with your index finger to form a pocket.
5. Hold the dropper (tip down) with the other hand, as close to the eye as possible without touching it.
6. While looking up, gently squeeze the dropper so that a single drop falls into the pocket made by the lower eyelid. Remove your index finger from the lower eyelid.
7. Close your eye for 2 to 3 minutes and tip your head down as though looking at the floor. Try not to blink or squeeze your eyelids.
8. Place a finger on the tear duct and apply gentle pressure.

The subject should repeat the above procedures for the other eye to demonstrate to the Investigator or designee that they are able to perform the drug administration satisfactorily. Subjects will be instructed to perform these steps on each administration of the study medication. Instructions for use will be provided to the subjects with the study drug and site personnel will ensure that these instructions are given to the subject.

5.5 Subject

5.6 Monitoring

Subjects will receive their first dose of study drug on study Day 1 in the doctor's office and after completion of the study assessments will have the topical eye drops dispensed for self-administration.

Subjects will be provided with diaries to record the time of each dose and will also be asked to record any adverse symptoms. In addition, they will be asked to make a note of any missed doses together with the reason for the omission. Subjects will be asked to bring their diaries with them at the 3, 6, 9 and 12 week visits. Diaries will be reviewed with the subject by a member of the research team at each visit. Additionally, subjects will be asked to bring back the used and unused drug eye droppers at each study visit. Participants will be asked to return the unused eye droppers each study visit as a method to determine compliance.

5.7 Prior and Concomitant Therapy

Prior medications are defined as all medications taken within 30 days prior to Day 1, whether there is continued use or not. Concomitant medications must be identified in the subject's medical record, including all lubricants administered for DED. These medications will be recorded in the case report form (CRF).

• For each medication taken, the following information will be collected:

1. Medication trade name
2. Eye that was treated, if applicable
3. Indication for which the medication was given
4. Date started
5. Date stopped
6. Dose of medication used.

Subjects will be permitted to continue their chronic DED treatments which may include the use of artificial tears, cyclosporine, corticosteroids, eyelid massage, contact lens, or warm compresses. The number of drops and frequency must be recorded in the subject diary provided.

• The use of any investigational agent during past 30 days is prohibited.

The subjects will be monitored frequently (at weekly intervals) to ensure that they are not subjected to any undue risks during the course of the study. Additionally, they will be warned of the possible signs and symptoms of clinical worsening of DED, and advised to contact the research team immediately in case any of those symptoms occur. Subjects will also be encouraged to contact the research team in case they experience any ocular discomfort during the course of the study. The subject's condition will be monitored by the physician (Principal Investigator) at each study visit, as well as at any interim visit (in case of adverse symptoms, as mentioned above). Any worsening of DED or any adverse event due to the study drug will be recorded. In case of clinical worsening, based on the individual subject's clinical condition, one or more of the following therapeutic decisions may be implemented: (1) Increasing the frequency of use of artificial tears, or other dry eye therapy (Restasis/ corticosteroids), (2) Withdrawal of the use of study drug. The decision will be made by the physician (Principal Investigator) based his clinical judgment as per the individual subject's clinical condition. After any clinical worsening is noted, the subjects will be followed closely (at least weekly) until complete resolution of symptoms and return to the subject's previous baseline.

5.8 Rescue Plan

Subjects will be monitored by the Principal Investigator at each study visit. Any worsening of DED or any adverse event (AEs) will be recorded, and in the case of AEs, followed to resolution. In case of clinical worsening/ adverse event(s), based on the individual subject's clinical condition, one or more of the following therapeutic decisions may be implemented:

(1) Increasing the frequency of artificial tears/ other dry eye treatments, and/ or

(2) Discontinue the study drug.

The decision will be made by the Principal Investigator based on his clinical judgment and the individual subject's clinical condition. The subject shall receive the treatment required for his/ her eye condition as per established clinical guidelines.

5.9 Packaging

The study drug will be dispensed from the UIC Eye and Ear Infirmary (EEI) Pharmacy. No modifications will be made to the study drug constituents or its packaging. The drug will be dispensed as is marketed for ophthalmic use (5 mL in 8 mL eye dropper bottles). A label with abbreviated study name will be placed on each eye dropper bottle. It will include the subject's name, instructions for drug use and storage and the drug expiration date. The label will also include the study name (abbreviated) and a statement that the drug is "**investigational** for use only in this research study." The dispensing will be done at Illinois eye and ear infirmary (EEI) pharmacy. The eye dropper bottles will be used by subjects as multiple-dose applications.
The first dose will be administered to the subject by the researcher at the first treatment visit (visit 2, day 1). No separate packing will be done for the study medication to be used in the MD's office.

5.10 Receiving, Storage, Dispensing and Return

5.10.1 Receipt of Drug Supplies

The UIC Investigational Drug Service (IDS) will order the study drug. The study drug will be stored in the Taylor Street/ EEI pharmacy and dispensed to subjects as needed.

5.10.2 Storage

Study drug will be stored at EEI pharmacy until such time as a subject visit is scheduled. The study drug will be directly dispensed to the subject from the EEI pharmacy on each treatment visit. The study drug will not be stored in the MD's office, except when a subject receives his/her first dose, when the medication may be kept in the MD's office for a maximum of 2- 3 hrs.

5.10.3 Dispensing of Study Drug

At the first treatment visit (day 1), the first study medication dose will be administered to the subjects in the clinic and the eye dropper bottle containing sufficient drug to last for 3 weeks will be given to them to take home. The subjects will be asked to return the used eye dropper bottle at the follow- up visits. We will then retrieve the previously –dispensed eye dropper bottle and a fresh 3 week supply will be dispensed by the pharmacy. This will continue from week 3 to week 12. No new drug eye dropper bottle will be given on the 6th (week 12) visit.

5.10.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug ordered/ received, drug consumed, and drug remaining. Any discrepancies will be investigated, resolved, and documented. The used drug eye droppers will finally be disposed by the pharmacy according to the pharmacy standard protocols.

6 Study Procedures

6.1 Subject Recruitment and Screening

Prior to recruitment of any subjects into the study, written approval of the protocol and informed consent will be obtained from the Institutional Review Board (IRB).

Potential subjects will be recruited from the clinical practice of the investigator at the time of their routine eye examination visit. The clinical practice is located at the Department of Ophthalmology and Visual Sciences, Eye and Ear Infirmary, 1855 W. Taylor Street, Chicago IL 60612. Patients with MGD will be approached by a member of the research staff to determine if the subject might be interested in participating in a research study. If the subject is interested, the research staff member will describe the study. If the subject is willing to enter the study, the study will be discussed and the subject will be asked to sign the informed consent form. Subjects will be screened for eligibility, as per the inclusion/ exclusion criteria, and as detailed in section 6.5.1. Eligible subjects will be enrolled in the study.

6.2 Assignment of Subject Identification

A study identification (ID) number will be assigned to each subject at enrollment. This study ID number will be used on all study-related documents. To maintain confidentiality, the subject's name will not be recorded on any study document other than the informed consent and patient case report forms. The master code list will link the subject MRN to the study ID number given to each subject. The master code list will be stored on the desktop in PI's Office/ Lab in Lions of Illinois Eye Research Institute (LIERI). The data collected and master code list will be accessible only to the PI and the research team involved in this project. The desktops will be password protected as well. Data will not be shared over the internet and will remain password protected. Confidentiality will be maintained. Data will be de-identified once study is completed and for subjects determined to not meet eligibility criteria or who later decline participation in the consent process.

6.3 Screen Failure

A record of screen failures and the reasons for non-eligibility to the study will be maintained.

6.4 Subject Enrollment

Subjects meeting the enrollment criteria (see Sections 4.1 and 4.2) will be eligible for the study.

6.5 Study Assessments

The following detailed procedures are performed at the designated clinic visit. All results will be documented on the subject's medical/research charts, source documents, and CRFs as required. All ophthalmic procedures will be performed on both eyes.

6.5.1 Visit 1 Screening
Day -7 to 0

After obtaining informed consent, the following assessments will be performed within fourteen days prior to the subject receiving the first dose of study medication:

- Demographic information including: birth date, gender, race and ethnic origin.
- Medical History including prior medication use and prior procedures: Medical history will be obtained by interviewing the subject and will include a review of the following systems: cardiovascular, dermatologic, gastrointestinal, genitourinary, musculoskeletal, neurologic and respiratory. Any history of cerebral or coronary insufficiency, postural hypotension or Raynaud's disease will be noted. An allergic history (including medications and food), substance abuse history (including alcohol) and a history of medication use (including prescription, OTC, and herbal products) during the past 30 days will also be completed.

- Ophthalmic history including: date when the MGD began, verification that the subject has MGD, medications used by the subject to treat MGD, previous procedures to treat MGD. Ocular symptoms due to dry eyes will be quantified using the Ocular Surface Disease Index (OSDI) i (section 3.3.2).
- Ophthalmic Examination (slit lamp examination, Ocular Surface Redness Score, Rose Bengal staining, and a Schirmer 1 test). Eyelid margins and meibomian gland openings will be evaluated during a slit lamp examination by the physician; and changes such as no. of and morphological alteration (capping/ obliteration) of meibomian gland orifices, lid margin vascularizatuion (including telangiectasia and muco-cutaneous anastomosis), lid margin hyperkeratinization, irregularity and muco-cutaneous junction shift, expressivity of meibum by meibomian glands and quality of expressed meibum, will be recorded. The number of visible meibomian gland openings on each eye lid will be counted manually during a slit lamp examination of the eyes. Extent of lid margin vascularization and staining of ocular surface and eye lids using the rose Bengal/ fluorescein dye will also be recorded. External eye photographs (including eye lids) will be taken for recording redness and other lid margin disease.

- Pregnancy test (urine), if applicable. Women of reproductive age will be asked to use a method of birth control that is acceptable to the subject and the study doctor. This may include oral contraceptive pills, birth control implants/shots or patches, barrier methods or abstinence. Women of reproductive age will not be included in the study if they refuse to use any birth control measure, including abstinence.

6.5.2 Visit 2 Day 1 *(Randomization and First treatment visit)*

Prior to first dose (Baseline)

- Vital Signs (blood pressure taken while subject is relaxed in a sitting position for at least 3 minutes, pulse, and temperature)
- BSCVA (Snellen's chart)
- OSDI
- Schirmer 1 test and Rose Bengal staining
- Keratograph Oculus Redness Score
  > Non-invasive Keratography Tear Film Break-up Time (NIKBUT)
  > Tear Meniscus Height (TMH)
- TearLab Osmolarity Test
- LipiView II Examination
  > Lipid Layer Thickness (LLT)
  > Gland Drop Out Grade
  > Meibomian Gland Evaluator (MGE)
- Baseline Ophthalmic Examination (slit lamp examination, Ocular surface redness score)
- External eye and eye lids photographs

- Record changes in concomitant medication
- Adverse events since screening visit.

Investigator/designee administers first dose

Post-Dose

- Test Substance Tolerance (Visual Analogue Scale; VAS)
- Subjects will be trained on how to self-administer the study eye drops and be given a sufficient supply to last for 3 weeks, to take home.
- Subjects will receive a study diary on which to record the day/time of each dose and any adverse effects.
- Post dose evaluation for any adverse effects.

6.5.3 Visit 3: *Week 3 (± 2 days)*

Treatment Visit (after any dose for that day)

- Vital Signs
- BSCVA (Snellen's chart)
- OSDI
- Keratograph Oculus Redness Score
  > Non-invasive Keratography Tear Film Break-up Time (NIKBUT)
  > Tear Meniscus Height (TMH)
- Clinical Global Impression, Subject Global Assessment
- Test Substance Tolerance (VAS)
- Ophthalmic Examination (slit lamp examination, Ocular surface redness score)
- External eye and eye lids photographs
- Review the subject's diary and record changes in concomitant medication, deviations from drug schedule and adverse events.
- Subjects will be given study medication refill if they run out of the study drug.

6.5.4 Visit 4: *Week 6 (± 2 days)*

Treatment Visit (after any dose for that day)

- Vital Signs
- BSCVA (Snellen's chart)
- OSDI
- Keratograph Oculus Redness Score
  > Non-invasive Keratography Tear Film Break-up Time (NIKBUT)
  > Tear Meniscus Height (TMH)
- TearLab Osmolarity Test
- LipiView II Examination
  > Lipid Layer Thickness (LLT)
  > Gland Drop Out Grade
  > Meibomian Gland Evaluator (MGE)
- Clinical Global Impression, Subject Global Assessment
- Test Substance Tolerance (VAS)
- Ophthalmic Examination (slit lamp examination, Ocular surface redness score)
- External eye and eye lids photographs
- Review the subject's diary and record changes in concomitant medication, deviations from drug schedule and adverse events.

- Subjects will be given study medication refill if they run out of the study drug.

6.5.5 Visit 5: *Week 9 (± 2 days)*

Treatment Visit (after any dose for that day)

- Vital Signs
- BSCVA (Snellen's chart)
- OSDI
- Keratograph Oculus Redness Score
  > Non-invasive Keratography Tear Film Break-up Time (NIKBUT)
  > Tear Meniscus Height (TMH)
- Clinical Global Impression, Subject Global Assessment
- Test Substance Tolerance (VAS)
- Ophthalmic Examination (slit lamp examination, Ocular surface redness score)
- External eye and eye lids photographs
- Review the subject's diary and record changes in concomitant medication, deviations from drug schedule and adverse events.
- Subjects will be given study medication refill if they run out of the study drug.

6.5.6 Visit 6: *Week 12 (± 2 days)*

Treatment Visit (after any dose for that day)

- Vital Signs
- BSCVA (Snellen's chart)
- OSDI
- Rose Bengal staining, and Schirmer 1 test
- Keratograph Oculus Redness Score
  > Non-invasive Keratography Tear Film Break-up Time (NIKBUT)
  > Tear Meniscus Height (TMH)
- TearLab Osmolarity Test
- LipiView II Examination
  > Lipid Layer Thickness (LLT)
  > Gland Drop Out Grade
  > Meibomian Gland Evaluator (MGE)
- Clinical Global Impression, Subject Global Assessment
- Test Substance Tolerance (VAS)
- Ophthalmic Examination (slit lamp examination, Ocular surface redness score)
- External eye and eye lids photographs
- Review the subject's diary and record changes in concomitant medication, deviations from drug schedule and adverse events.

6.5.7 Visit 7: Week 15 (± 2 days)

Follow-Up Visit

- Vital Signs
- BSCVA (Snellen's chart)
- OSDI

- Clinical Global Impression, Subject Global Assessment
- Ophthalmic Examination (slit lamp examination, Ocular surface redness score)
- External eye and eye lids photographs
- Record changes in concomitant medication and adverse events.

7 Statistical Plan

7.1 Sample Size Determination

The sample size is based on the primary efficacy end point (mean OSDI baseline and 12 weeks score) using the following assumptions: (i) mean ODSI score in chronic oGVHD population = 21.66 (ii) sigma (standard deviation) = 11.35. The OSDI (mean and sd) assumptions are based on Agomo EU, et al [33] in chronic ocular GVHD patients. In this study, pre-transplant OSDI score were 1.52 ± 3.14 and in chronic ocular GVHD OSDI score were 21.66 ± 11.35. A total of 51 subjects will be required to detect the difference between groups using a Wilcoxon test with an alpha level of 0.05 and 80% power. We elected to enroll 17 subjects per group.

7.2 Statistical Methods

One eye (target eye) will be selected at screening visit for statistical comparisons as follows: (i) if only 1 eye meets inclusion criteria, this eye is used; (ii) if both eyes meet inclusion criteria, the eye with the higher RBS score is used; (iii) if both eyes have the same RBS score, then the one with the lower Schirmer I score is used; (iv) if both eyes have same scores, the right eye is used. Secondary analyses will be performed for the non-target eye as well. Descriptive statistics will be used for all primary and safety endpoints, when appropriate.

A Wilcoxon test will be used to compare changes in signs and symptoms from baseline to follow-up values at Week 3, Week 6, Week 9, Week 12 and Week 15.

7.3 Subject Population(s) for Analysis

Subject population for analysis will include all-treated population: Any subject enrolled in the study who received at least one dose of study drug will be analyzed.

8 Safety and Adverse Events

8.1 Adverse Event Definitions

The following are specific definitions of terms guided by the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) and the U.S. Code of Federal Regulations that apply to this section:

Adverse Event: Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can be any unfavorable sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

Subjects will be reminded to inform the study staff of any adverse effects that they have experienced or are experiencing after the first administration of study drug. In addition, subjects will record adverse events in their diary throughout the study. All reports of adverse events during the study will be

recorded on an Adverse Event Case Report Form (CRF). The subject should not be prompted about any adverse events that may occur during this trial.

For each adverse event, the following information will be recorded on the subject's Case Report Form(s): onset date, end date or continues, intensity, duration, relationship to test patch, action taken, and outcome. If a subject experiences a serious adverse event (SAE), study staff may discontinue the subject from study participation. The study staff must notify the IRB within 24 hours of receipt of the information. The study staff will instruct the subject to notify the research facility should any adverse event occur within 7 days of study completion. (For definitions of an AE and SAE, see below). Subjects who withdraw due to an adverse event may be replaced.

• ***Serious Adverse Event:*** An untoward medical occurrence that at any dose:

1. results in death
2. is life-threatening
3. requires inpatient hospitalization or prolongs existing hospitalization
4. results in persistent or significant disability/incapacity
5. is a congenital anomaly/ birth defect
6. requires medical or surgical intervention to prevent any of the occurrences noted above.

• ***Life-threatening:*** Any adverse drug experience in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

• ***Unexpected adverse event:*** Any adverse event, the specificity or severity of which is not consistent with the current Investigator's Brochure.

8.2 Classification of Adverse Events by Severity

All toxicities/adverse events will be graded according to the following definitions to code the intensity of the event.

Mild: Usually transient, requiring no special treatment, and does not interfere with the subject's daily activities.

Moderate: Traditionally introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually relieved by simple therapeutic measures.

Severe: Causes an interruption of the subject's usual daily activity and traditionally required systemic drug therapy or other treatment.

Note: If the intensity of an adverse event changes, the event will be reentered as a separate event.

There is a distinction between the severity and the seriousness of an adverse event. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a serious adverse event. For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for serious adverse events listed previously.

8.3 Classification of Adverse Events by Relationship to Study Treatment

The relationship or association of the study medication to an adverse event, as causing or contributing to the adverse event, will be characterized as defined below:

Probable: The adverse event follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and the possibilities of factors other than the drug, such as underlying disease, concomitant drugs or concurrent treatment, can be excluded.

Possible: The adverse event follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and the possibility that drug involvement cannot be excluded, e.g. existence of similar reports attributable to the suspected drug, its analog or its pharmacological effect. However, other factors such as underlying disease, concomitant drugs or concurrent treatment are presumable.

Not Related: The adverse event has no temporal sequence from administration of the drug, or it can be explained by other factors, including underlying disease, concomitant drugs or concurrent treatment.

8.4 Action(s) Taken

One or more of the following will be recorded by the Investigator for each adverse event:

- No action taken
- Discontinued study drug (Subject withdrawn due to this adverse event)
- Administered therapy
- Hospitalized subject (due to this adverse event)
- Other (specify) - includes tests, labs confirming reaction

8.5 Outcome

The status of each adverse event will be recorded as follows, if applicable: SAE: Indicates that the adverse event met the criteria of a serious adverse event (SAE) and the SAE was reported to the IRB. Caused Withdrawal: Indicates that the adverse event caused the subject's withdrawal from the study.

8.6 Adverse Event Reporting

All subjects who have been exposed to study drug will be evaluated for adverse events. Adverse events will be recorded starting after the first dose of study drug and continuing until the end of the study. All adverse events will be evaluated beginning with onset, and evaluation will continue until resolution is noted, or until the Investigator determines that the subject's condition is stable, whichever is earlier. The Investigator will take all appropriate and necessary therapeutic measures required for resolution of the adverse event. Any medication necessary for the treatment of an adverse event must be recorded on the concomitant medication case report form. If more than one distinct adverse event occurs, each event should be recorded separately. Procedures such as surgery should not be recorded as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of adverse event as described previously.

8.7 Serious Adverse Event Reporting

All Serious Adverse Events (SAE) that occur during the course of the study, including death, which are unanticipated require reporting to the IRB within **5 business** days of the investigator becoming aware.

Serious adverse events will be recorded starting after first dose of study drug and continuing until the end of the study. The minimum information to be provided includes:

1. Protocol Number
2. Initial reporter
3. Subject identification
4. Nature and date of the event/effect
5. Country of the event/effect
6. Severity of the event/effect
7. Reporting criteria
8. Narrative description of the event/effect
9. Outcome if known
10. Causal relationship to the investigational product
11. Additional and follow-up information as requested by the medical monitor.

Events requiring reporting to the IRB within **15 business days** of the investigator becoming aware include:

1. Local adverse events or problems that are unanticipated and, while not meeting the criteria of serious, indicate research is associated with a greater risk of harm to participants or others than previously known.
2. New information indicating an unexpected change to the risks or benefits of the research (i.e., an unanticipated problem).
3. Administrative hold by investigator, regulatory authorities or other entities.

8.8 In Case of an Emergency

In medical emergencies, the Investigator should use medical judgment and remove the subject from immediate hazard. The IRB should be notified as to the type of emergency and the course of action taken. The CRF and the source document for the subject must describe the departure from the protocol and state the reason.

8.9 Data Safety Management Plan

The study protocol will be reviewed and approved by the UIC IRB. Adverse events and compliance will be monitored. Research staff will be trained on the protocol requirements and data collection methods before completing study related procedures. **Privacy, coding, storage:** Research staff will be trained on the protocol requirements and data collection methods before completing study related procedures. Random study ID numbers will be assigned to study subjects. A master code list will link the subject MRN to the study ID number. The data collected will be stored on PI's desktop in a HIPPA compliant encrypted folder at the Ear and Eye Infirmary and Lions Eye Research building. The data collected, master code list will be accessible only to the PI and the research team involved in this project. The desktops will be password protected as well.

All Serious Adverse Events (SAE) that occur during the course of the study, and possibly related to the study intervention, including death, which are unanticipated will be reported to the IRB within 5 business days of the investigator becoming aware. A copy of the report will be sent to the FDA.

Events requiring reporting to the IRB within 15 business days of the investigator becoming aware include;

• Local adverse events or problems that are unanticipated and, while not meeting the criteria of serious, indicate research is associated with a greater risk of harm to participants or others than previously known.
• New information indicating an unexpected change to the risks or benefits of the research (i.e., an unanticipated problem).
A copy of this report will be sent to the FDA.

The minimum information to be provided includes:

1. Protocol Number
2. Initial reporter
3. Subject identification
4. Nature and date of the event/effect
5. Country of the event/effect
6. Severity of the event/effect
7. Reporting criteria
8. Narrative description of the event/effect
9. Outcome if known
10. Causal relationship to the investigational product
11. Additional and follow-up information as requested by the medical monitor.

8.10 Study Oversight

The Study PI has primary oversight responsibility for this study. Sandeep Jain, MD is a board certified Ophthalmologist with an active practice in the area of Dry Eye Disease, including those with Meibomian Gland Disease. He routinely takes care of patients with severe ocular surface disease. He's also the director of Dry Eye service at UIC. Therefore, he's well qualified to recognize the symptoms and clinical signs of an adverse event. Dr. Jain has been the PI of past and active IRB approved clinical studies and has monitored data related to those studies. Therefore, he has experience in data and safety monitoring.

The Principal Investigator and his research team are responsible for identifying adverse events. Safety monitoring will include careful assessment and appropriate reporting of adverse events. Subjects will be reminded to inform the study staff of any adverse effects that they have experienced or are experiencing after the first administration of study drug. Subjects will be provided with diaries to record at home the time of each dose and any adverse symptoms. All reports of adverse events during the study will be recorded on an Adverse Event Case Report Form (CRF). In addition, subjects will be asked to make a note of any missed doses together with the reason for the omission. A member of the research staff will review diary entries with the subject at each study visit. Subjects will be asked to bring back the left-over drug at each study visit. The amount of drug remaining in the used vial will also give an estimate of the compliance.

Accumulated safety and data information will be reviewed at 3 weeks for 10 subjects. The research team will then evaluate whether it is safe to proceed with the study, and if the protocol or informed consent documents require revision based on that review.

9 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.1 Records Retention

It is the investigator's responsibility to retain study essential documents. Research file documents will be uniformly held indefinitely after the closure of the research file per UIC IRB requirements.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. The study may not commence until IRB approval is granted.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally authorized representative, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

Departmental funds have been committed to the Corneal Neurobiology Laboratory. Also, Ocugen is partially funding this research. For the release of funds, they will have access to some study data. We will email Ocugen the enrollment updates and clinical visit logs at regular intervals. The data emailed to Ocugen will be linked with a code. Only the PI, and Key Research personnel listed in Appendix P will have access to the linked code. PHI and sensitive identifiable data will not be shared via email with any entity. Ocugen may also inspect records relevant to the study, to ensure compliance with the terms of agreement between the study PI and Ocugen. Any inspection of study records by Ocugen will be performed on site only (here at UIC).

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan. All UIC investigators will follow the University conflict of interest policy.

12.3 Subject Stipends or Payment

$50/ visit will be given to each patient on baseline visit and on the five subsequent visits afterwards till week 15 to offset to some extent their parking/transportation expenses. The total amount of compensation will be $300.

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